REMARKS

In the amendments above, Claims 1, 6, 9, 13, 14, 17-19 and 27-29 have been newly cancelled, Claims 12, 22, 26, 30, and 31 have been amended, and new Claims 32-35 have been added, to more particularly point out and distinctly claim Applicants' invention. Support for the amendments to Claim 12 may be found in cancelled Claims 13, 14, and 17-19. Support for new Claim 32 may be found on page 4, lines 18-19, of the application as originally filed. Support for Claims 34 and 35 may be found on page 7, lines 1-5.

35 U.S.C. § 101 and 35 U.S.C. §112 Rejections

In the Office Action dated October 29, 2007, the Examiner rejected Claim 27 under 35 U.S.C. § 101 because the claimed invention is allegedly not supported by a credible asserted utility or a well established utility. More specifically, the Examiner maintained that Claim 27 is directed to a method of preventing bacterial or protozoan infection. The Examiner maintained that the broadest reasonable interpretation of the term infection merely requires that one microorganism gain entry into the cells of a host. The Examiner maintained that there is no evidence that entry would be prevented, therefore that utility would not be credible.

The Examiner also rejected Claim 27 under 35 U.S.C. § 112, first paragraph. More specifically, the Examiner maintained that the claimed invention is not supported by either a credible asserted utility or a well established utility for the reasons set forth above, one skilled in the art would not know how to use the claimed invention.

Applicants have cancelled Claim 27, making the rejection under §112 moot. Applicants have further amended Claim 26 to include a method of treatment of bacterial or protozoan pathology in a mammal, comprising administering an effective amount of azithromycin hydrogen citrate salt to the patient requiring antibacterial or antiprotozoan therapy. Applicants note that, as shown on page 7, lines 24-30, the azithromycin

hydrogen citrate salt of the present invention is useful as an antibacterial and an antiprotozoan agent and can be administered orally, parenterally, topically or rectally in the treatment of a patient requiring antibacterial or antiprotozoan therapy.

35 U.S.C. § 102(b) and 35 U.S.C. §103(a) Rejections

The Examiner further rejected Claims 1, 6, 9, 12-17, 22, 26-28, 30 and 31 under 35 U.S.C. § 102(b) as being anticipated by Asero et al., U.S. Patent No. 6,277,829 ("Asero") or Khamar et al., PCT Published Patent Application No. WO 02/07736 ("Khamar"). The Examiner maintains that Asero discloses the claimed formulation comprising azithromycin and citric acid wherein the molar ratio of azithromycin to citric acid is about 1:0.67 to 1:1.5 and the pH is adjusted to 5.5-7.6 (column 3, lines 51-57) and having a concentration of 10% (column 4, lines 1-2); that Khamar discloses dissolving citric acid in water, adjusting the pH to 4 to 6 and adding azithromycin (page 4, Example 1); and that an addition salt comprising azithromycin and citric acid would have been inherently formed from such a process.

The Examiner rejected Claims 1, 6, 9, 12-19, 22, and 26-31 under 35 U.S.C. § 103(a) as being unpatentable over Asero or Khamar. The Examiner maintains that each of Asero and Khamar discloses combining citric acid and azithromycin but does not disclose isolation of azithromycin hydrogen citrate by crystallization and that, since crystalline azithromycin is well known in the art, such as azithromycin dehydrate disclosed by Khamar, a person having ordinary skill in the art at the time the claimed invention was made would have been motivated to crystallize the citric salt of azithromycin because said salt would have been expected to possess similar properties as known crystalline forms of azithromycin.

Applicants respectfully traverse the rejections.

Applicants have amended the claims herein to further clarify their scope. Applicants note that product Claims 1-9, as originally filed, were directed to an assay for

testing the solid obtained salt. The assay consisted of dissolving the solid salt in a 10% aqueous solution and measuring the pH of the solution, without changing it, by the addition of any component to the solution. Therefore, in the solution, there is only the specific salt and the water and nothing else. The 10% aqueous solution of said specific salt provides a pH close to 5.

Applicants have amended Claim 12 and have added new Claim 34, directed to and supported by the original application as filed. Applicants note that on page 7, lines 1-5, of the application as originally filed, it is stated that "[t]he X-ray diffraction, carbon 13 nuclear magnetic resonance (^{13}C-NMR) in solid state and IR spectra serve to identify the azithromycin hydrogen citrate in accordance with the first aspect of the invention. See Figures 1 to 9." The specific salt, "azithromycin hydrogen citrate salt," was not present in the cited prior art. The specific azithromycin hydrogen citrate salt obtained in a solid state has unexpected properties over the known compound, azithromycin. Applicants have amended the claims to highlight these unexpected properties.

Claim 12 is directed to a process for preparing and isolating the azithromycin hydrogen citrate salt in a solid state by reacting azithromycin basic groups dissolved in a solvent with the acid groups of citric acid added to said solution as the only ingredients. (See page 6, lines 24-35, and Examples 1 to 3). At a molar ratio of azithromycin to citric acid in the solution close to the stoichiometric ratio, the azithromycin hydrogen citrate salt of the subject invention is formed without adjusting the pH to a particular range. The resulting salt is isolated by crystallization in the conditions given in Claim 12. This solid salt may contain a residual content of solvent and a low content of water.

Neither Asero nor Khamar discloses the salt of the present invention or the process of attaining the salt of the present invention. Asero discloses a process for preparing an aqueous formulation for ophthalmic use containing azithromycin. The object of Asero is to provide stable aqueous formulations for antimicrobial ophthalmic therapy. As stated on Column 3, lines 44-58, of Asero, the solution containing azithromycin, citric acid, and

the acceptable polybasic phosphate must be adjusted to a value of 5.5 to 7.6 in order to achieve a stable aqueous formulation. In Figure 3, it is shown that formulations of the invention are stable at a pH of 6.4 to 8.7. However, Asero also seeks an antimicrobial ophthalmic formulation and discloses, in the last paragraph of Column 10, that the ophthalmic solutions are affected by pH and that an appropriate pH range needs to be selected wherein the ophthalmic solutions will still be effective to inhibit the activity of azithromycin against pathogens causing ocular infections. Example 5, "In vitro antibacterial activity," teaches azithromycin solutions at pHs 6.5, 7.2, and 7.8. Therefore, the step of adjusting the pH to the range from 5.5 to 7.6 is an essential feature in the process described by Asero.

The process described by Asero for the preparation of an aqueous ophthalmic formulation containing azithromycin also comprises other ingredients in the solution such as polybasic phosphate. (See Example 1). The presence of additional ingredients in the solution modifies the pH of said solution, which prevents the basic groups of azithromycin from reacting with the acid groups of citric acid. Applicants have previously emphasized that dibasic disodium hydrogen phosphate used in the process of Asero will react with azithromycin.

Claim 12, as currently amended, is directed to a process for obtaining a specific salt of azithromycin in a solid state, which does not require adjustment of the pH to a particular range in order to be stable and to maintain antimicrobial activity. Further, no additional components are needed for preparing the specific claimed salt.

Khamar teaches a clear liquid pharmaceutical composition of azithromycin. Khamar discloses, on page 3, second paragraph, that the method for preparing the clear liquid pharmaceutical compositions of azithromycin is made possible by solubilizing azithromycin in water at a pH of 4.0 to 6.0 and then adding sodium hydroxide, thereby changing the pH between 6.0 and 7.0.

As in the method taught by Asero, Khamar's method also requires the pH value of the solution to be adjusted to a higher pH value, between 5.5 to 7.0, in order to achieve an azithromycin liquid composition stable for longer periods. (See page 3, third paragraph). In particular, Khamar states that when a solution is prepared using azithromycin at a pH between 4.0 and 6.0, it does not remain stable for a long term and thus, the pharmaceutical composition is not stable.

As noted above, the methods of both Asero and Khamar require that the pH of the solution containing azithromycin be adjusted in order to obtain a product that will be stable for a long term and that maintains antibacterial activity.

Furthermore, the process as taught by Khamar requires that an extra ingredient, sodium hydroxide, be added to the solution, thus forming monosodic salt of citric acid and raising the pH of the solution. This prevents the basic groups of azithromycin from reacting with the acid groups of citric acid. Although a salt of azithromycin may be formed, the salt will be different than the salt of the present invention.

Neither Asero nor Khamar discloses the claimed formulation of azithromycin hydrogen citrate salt which is characterized by X-ray diffraction, Carbon 13 nuclear magnetic resonance (^{13}C-NMR) in solid state and IR spectra. The differences between the subject matter of the present invention and the prior art are such that the subject matter as a whole would not have been obvious at the time the invention was made to a person having ordinary skill in the art.

Furthermore, the azithromycin hydrogen citrate salt, according to the present invention, has a high stability in solid phase compared with azithromycin and/or azithromycin citrate salt at room temperature and 80°C.

Applicants attach a study authored by one of the inventors, Antonio Cosme Gomez, along with a Declaration establishing that, contrary to the indications made in Asero and Khamar, the azithromycin hydrogen citrate salt of the present invention is

stable and, further, that the pH is not adjusted to achieve the product. In the set of assays described on page 2, lines 14-17, of the study, it is shown that new acid addition salts (azithromycin hydrogen citrate salt) are soluble in aqueous medium and at the same time have suitable stability properties in a solid phase in a solution. The assays corroborate the content of the application as filed.

In view of the comments above and the amendments to the claims, it should be clearly appreciated that the claims herein are patentable over Khamar and Asero. Accordingly, withdrawal of the rejections and allowance of the claims is believed proper.

Reconsideration and allowance of all the claims herein are respectfully requested.

Respectfully submitted,

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